REMARKS

Claims 1-12, 20-22, 27-31, 35 and 36 currently appear in this application. The Office Action of June 21, 2006, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Specification

The specification is objected to because the disclosure is said to contain many formulas that are not legible.

Submitted herewith are copies of pages 8-12 and 37-44 showing all of the bonds in the formulae. No new matter is enclosed, and none is intended.

The alleged hyperlink at page 36, line 10, is not an embedded hyperlink because it is not between the symbols "<>" and does not include http://. Accordingly, it has not been deleted from the specification.

Rejections under 35 U.S.C. 112

Claims 13-20, 23-26, 32-34 and 37-41 are rejected under 35 U.S.C. 112, first paragraph.

The present amendment cancels claims 13-19, 23-26, 32-34 and 37-41, so that this rejection is now moot.

Claims 2, 3, 13-20, 23-26, 29-34 and 37-41 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement. The claims are said to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

This rejection is respectfully traversed. Claims 2 and 3 have been amended to correct self-evident typographical errors. Claims 29 and 30 ultimately depend from claim 2 and claim 31 depends from claim 3. Claims 13-19, 23-26, 32-34 and 37-41 have been cancelled, so this rejection with respect to these claims is now moot.

Claim 20 is a claim for a pharmaceutical composition rather than a method for treatment and therefore complies with the enablement requirement. The composition contains compound as described in the specification.

Claims 10 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

This rejection is respectfully traversed. Claim 10 has been amended to depend from claim 9, and the limitation "wherein R^6 is H" has been added to claim 9 to provide antecedent basis for the recitation in claim 10. Support for this amendment can be found in the specification as filed at page 9, line 22.

Claims 27 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

This rejection is respectfully traversed. Claims 27 and 28 have been amended to recite "compound."

Claims 1, 27, 28, 31 and 35-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. The claims have been amended to recite "compound" rather than "compounds."

The Examiner states, "at no time is Y substituted by (C=O)N(R,R')." However, claim 1 recites, "Y within formula I is a substituted or unsubstituted piperidino moiety", and the definition of "substituted" on page 7, lines 10-22 includes

"aminocarbonyl" at line 16. Therefore, Y can be substituted by (C=O)N(R,R'), so this proviso is necessary.

Claims 1-3, 5-10, 20-22, 27-31 and 35-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. The claims have been amended to recite the singular "compound" rather than the plural "compounds."

Claims 3, 9 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The definition of L^1 and L^2 wherein L^1 and L^2 are C_1-C_6 aliphatic alkyl is not described in the specification.

This rejection is respectfully traversed. Claims 3 and 9 have been amended to delete "aliphatic." Claim 31 depends from claim 3.

Claims 2, 3, 5-7, 10, 13-15 and 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

This rejection is respectfully traversed. With respect to claims 2, 29 and 30, the phrase "a 4-8 membered

saturated cyclic alkyl containing one or two nitrogen atoms" has been deleted.

Claim 3 from which claim 31 depends, has been amended to recite "alkyl and" rather than "alkyland."

Claim 3 from which claim 31 depends, has been amended to recite "sulfonyl and" rather than "sulfonyland."

Claim 5 from which claims 7 and 35 depend, has been amended to recite "sulfonyl and" rather than "sulfonyland."

Claim 10, from which claim 36 depends, has been amended to recite "alkyl" rather than "alkyland."

Claims 13-15 and 32-24 have been cancelled by the present amendment.

Claim 35 has been amended to recite "C_1-C_6 alkyl group" rather than "C_1-C_4 alkyl group."

The Examiner alleges that there is insufficient antecedent basis for the limitation "a triazole ring which is fused with an unsubstituted or substituted aryl or heteroaryl" for the definition of L^1 in claim 36. Since claim 10, from which claim 36 depends, has been amended to depend from claim 9, it is believed that there is sufficient antecedent basis for this recitation of L^1.

Art Rejections

Claims 1-3, 13-20, 23-27, 29, 31-33 and 37-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobs et al., U.S. Patent No. 6,399,603.

This rejection is respectfully traversed. The claims have been amended to exclude compounds wherein neither Ar^2 is 1,3-phenylene or 1,4-phenylene.

Claims 1-3 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinto et al., U.S. Patent No. 6,020,357.

This rejection is respectfully traversed. The claims have been amended to exclude compounds wherein Ar^2 is not 1,4-phenylene.

Claims 1-3, 5, 6, 13-18, 20, 24, 25, 32, 37, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Chandrakumar et al., U.S. Patent No. 5,843,906.

This rejection is respectfully traversed. The claims have been amended to exclude compounds wherein Ar^2 is 1,3-phenylene.

Claims 1, 3, 5, 6, 8, 9, 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Grigoryan et al., *Armyanskii Khimicheskii Zhurnal*, 1984 **18(1)**:58-51, CAPLUS abstract.

This rejection is respectfully traversed. The claims have been amended to exclude compounds in which Ar^2 is 1,4-phenylene.

Claims 1-3, 20 and 27-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaldrikyan et al., *Khimiko-Farmatsevticheskii Zhurnal* **18(1)**:58-61, 1984.

This rejection is respectfully traversed. The claims have been amended to exclude compounds in which Ar^2 is 1,4-phenylene.

Double Patenting

Claims 1-3, 5, 6, 13-35 and 37-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of copending application no. 10/381,197.

It is respectfully submitted that there has been no allowance of the claims of application no. 10/381,197. It is respectfully requested that this rejection be held in abeyance until it is known what claims are allowed, as it is entirely possible that allowed claims in application no. 10/381,197 will not render the present claims obvious.

Claims 1-3 and 5-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending application No. 10/381,200.

It is respectfully submitted that there has been no allowance of the claims of application no. 10/381,200. It is respectfully requested that this rejection be held in abeyance until it is known what claims are allowed, as it is entirely possible that allowed claims in application no. 10/381,200 will not render the present claims obvious.

Claims 1-3 and 5-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending application no. 10/381,665.

It is respectfully submitted that there has been no action on the claims of application no. 10/381,665. It is respectfully requested that this rejection be held in abeyance until it is known what claims, if any, are allowed, as it is entirely possible that allowed claims in application no. 10/381,665 will not render the present claims obvious.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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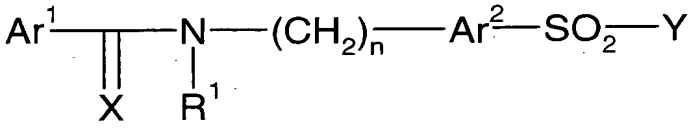
also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quarternary ammonium salt of the formula –NR,R',R" $^{+}$ Z^{-}, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

"Enantiomeric excess" (ee) refers to the products that are obtained by an essentially enantiomeric synthesis or a synthesis comprising an enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded. In the absence of an enantiomeric synthesis, racemic products are usually obtained that do however also have the inventive set out activity as JunK2 and/or 3 inhibitors.

Quite surprisingly, it was now found that sulfonamide derivatives according to formula I are suitable pharmaceutically active agents, by effectively modulating, in particular by down-regulating inhibiting the action of JNK's, notably of JNK 2 and/or 3.



I

The compounds of formula I according to the present invention being suitable pharmaceutical agents are those wherein

Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups,

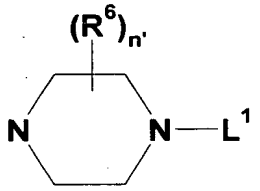
X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, preferably H, or R^1 forms a substituted or unsubstituted 5-6—membered saturated or non-saturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1.

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing the sulfonamide.

In a preferred embodiment of the present invention, Y is a piperidine or piperazine moiety according to the below formula



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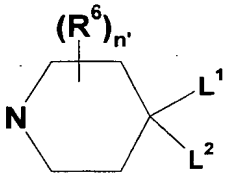
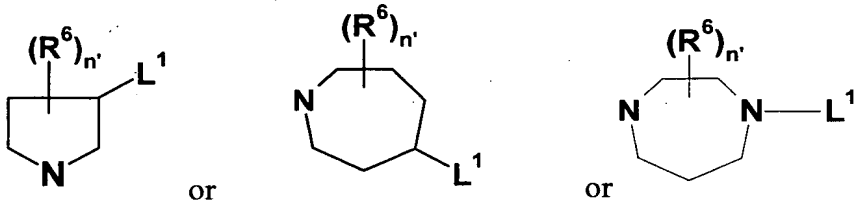


In said piperidine or piperazine groups, L^1 and L^2 are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$.

Thereby, R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), sulfoxy, acyloxy, thioalkoxy and n' is an integer from 0 to 4, preferably 1 or 2.

According to a further preferred embodiment of the present invention, Y is a pyrrolidine, an azepan or a 1,4-diazepan moiety of the below formulas



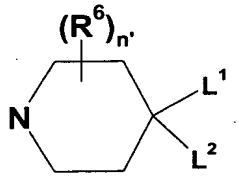
In said moieties, L^1 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$.

Thereby, R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), sulfoxy, acyloxy, thioalkoxy and n' is an integer from 0 to 4, preferably 0.

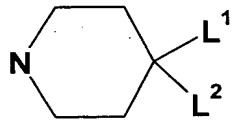
Most preferred azepan or a 1,4-diazepan moieties are those wherein , L^1 is -$NR^{3'}R^3$, with R^3 being hydrogen and $R^{3'}$ being a C_1-C_{12}, preferably C_4-C_6-alkyl which is optionally substituted with cycloalkyl, aryl or heteroaryl group.

All of the above mentioned aryl or heteroaryl groups could optionally be substituted by at least one of the groups selected from substituted or unsubstituted C_1-C_6-alkyl,like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, acyloxy, substituted or unsubsti-



whereby R^6, n', L^1 and L^2 are as above defined.

In a more preferred embodiment of the sulfonamide derivatives according to formula I, Ar^1 is 4-chlorophenyl, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl, Y is



whereby L^2 is H and L^1 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring, being preferably fused with a substituted or unsubstituted aryl group, e.g. a benzotriazole; or L^2 is -C(O)-R^3, or -NHR^3.

Thereby, R^3 is a substituent selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

Said aryl or heteroaryl groups may optionally be substituted by halogen, hydroxy, nitro, sulfonyl, e.g. a trifluoromethylsulfonyl group.

Specific examples of compounds of formula I include the following :

4-chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-chloro-N-({5-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[4-(4-fluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

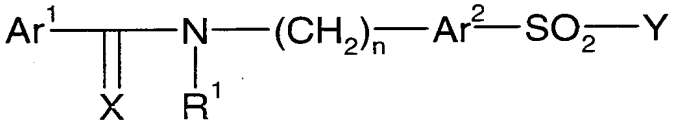
4-chloro-N-{[5-({4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-({5-[(4-{2-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide

group –C(=NH)-NH_2 (benzamidine) or a protected form thereof to be used as factor XA inhibitors (WO 99/16751).

- Two further compounds are rather incidentally disclosed in WO 97/45403 (i.e. 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine as selective dopamine D3 ligand) and in WO 97/30992 (i.e. N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride to be used for inhibiting farnesyl-protein transferase).
- Finally, compounds of formula I wherein X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, said Y being imperatively substituted by an amido group (C=O)N(R,R') at the alpha position of the sulfonamide nitrogen are disclosed within WO 98/ 53814. Said compounds are mentioned to be useful in the inhibition of cell adhesion.

Hence, the entirely novel sulfonamide derivatives are those of the below set out general formula I whereby the above identified known compounds are excluded.



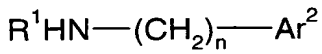
I

Still a further object of the present invention is a process for preparing the novel sulfamide derivatives according to formula I which have been set out above.

The sulfonamide derivatives of this invention can be prepared from readily available starting materials using the following general methods and procedures.

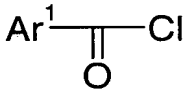
It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

In a preferred method of synthesis, the sulfonamide derivatives of the invention are prepared by first coupling an amine of formula II:



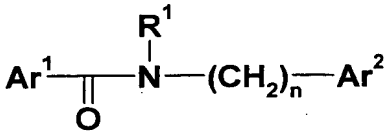
II

where Ar^2 and R^1 are as defined above, with an acyl chloride of formula III:



III

where Ar^1 is as defined above, to provide an amide of formula IV:



IV

Amines of formula II are either known compounds or can be prepared from known compounds by conventional procedures. Preferred amines as starting materials include thien-2-yl-methylamine, furan-2-yl-methylamine, pyridyl-2-ylmethylamine and the like. The acyl chlorides of formula III are also commercially available or previously described compounds. Preferred acyl chlorides include 4-chlorobenzoyl chloride, 4-fluorobenzoyl chloride, 4-trifluoromethylbenzoyl chloride and the like. If not known, the acid halide can be prepared by reacting the corresponding carboxylic acid with an inorganic acid halide, such as thionyl chloride, phosphorus trichloride or oxalyl chloride under conventional conditions.

Generally, this reaction is performed upon using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either in pure form or in an inert solvent, such as carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, as *N,N*-dimethylformamide, may also be used in this reaction.

When an acyl halide is employed in the coupling reaction, it is typically reacted with amine II in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, an excess of amine II may be used to scavenge the acid generated during the reaction.

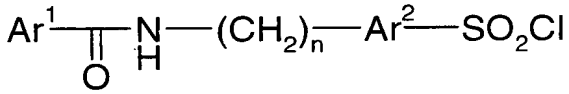
Alternatively, the carboxylic acid of compound III can be employed in the coupling reaction. The carboxylic acid of III are usually commercially available reagents or can be prepared by conventional procedures.

The coupling reaction of carboxylic acid of III (i.e. the acyl chloride) is conducted upon using any conventional coupling reagent including, for example, carbodiimides such as

dicyclohexylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide and other promoting agents, such as *N,N*-carbonyl-diimidazole or PyBOP. This reaction can be conducted with or without the use of well known additives such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. which are known to facilitate the coupling of carboxylic acids and amines.

The coupling reaction using either acid halide III or its carboxylic acid is preferably conducted at a temperature of from about 0°C to about 6°C for about 1 to about 24 hours. Typically, the reaction is conducted in an inert aprotic polar solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like using about 1 to about 5 molar equivalents of the amine based on the carboxylic acid or its acid halide. Upon completion of the reaction, the carboxamide IV is recovered by conventional methods including precipitation, chromatography, filtration, distillation and the like.

The sulfonyl chorides of formula V necessary for the preparation of the sulfonylpiperidines or piperazines of formula I are prepared using conventional sulfonating methods:



V

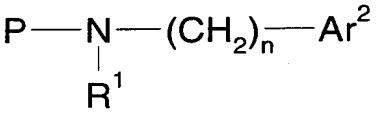
A preferred sulfonating reagent for use in this reaction is chlorosulfonic acid. Typically, the sulfonation reaction is performed by treating the carboxamide of formula (IV) with about 5 to about 10 molar equivalent of the sulfonating reagent in an inert solvent, such as dichloromethane, at a temperature ranging from about –70°C to about 50°C. Preferably, the addition of chlorosulfonic acid takes place at –70°C and leads to the formation of the intermediate sulfonic acid. Increasing the temperature to 20°C allows the formation of the sulfonyl chloride of formula V.

According to a further preferred method of preparation notably in case that the above pointed out method leading to the preliminary synthesis of sulfonyl chloride of formula V is not applicable, the sulfonyl piperidines and piperazines of this invention are prepared by the following steps:

- Protection of the amine function of compounds of formula II;
- Chlorosulfonylation of the aromatic group;
- Formation of the sulfonamide function;

- Deprotection of the protectiong group;
- Acylation of the above generated free amine;

Amines of formula II are protected with a suitable protecting group of an amine moiety to provide intermediate of formula VI wherein P denotes the protecting group.

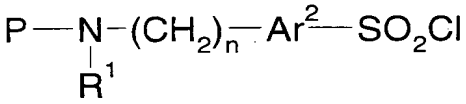


VI

Numerous protecting groups P of the amine function as well as their introduction and removal, are well described in T.W. Greene and G.M. Wuts, Protecting groups in Organic Synthesis, Third Edition, Wiley, New York, 1998, and references cited therein. Preferred are protecting groups that are acids and bases stable and can be further removed by using metal transition complexes such as palladium complexes, for example the allylcarbamate group (Alloc) or the N,N'-bisallyl group. Another preferred protecting group is the maleimide group which is stable in a all range of experimental conditions.

The introduction of said groups can be performed by reacting the corresponding bisallylcarbonate anhydride or allylbromide or maleic anhydride in the presence of a base such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like in an aprotic solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like at a temperature ranging from about 0°C to about 80°C.

Compounds of formula VI are then sulfonated using a conventional very mild sulfonating procedure that allows the obtention of sulfonyl chloride of formula VII.

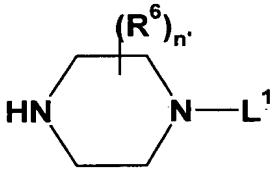


VII

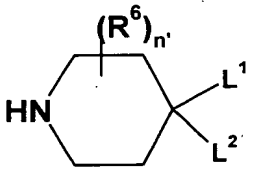
Typically, protected amine VI is treated with a base such as n-butyllithium or tert-butyllithium under an inert atmosphere, in a polar aprotic solvent such as tetrahydrofuran, ether or dioxane at a temperature ranging from –70°C to 0°C during a time ranging from 15 minutes to 4 hours. The so formed anion is then treated with SO_2Cl_2 or most preferably SO_2 by bubbling the gas into the reaction mixture at a temperature ranging from –

70°C to 20°C during a time ranging from 5 minutes to 1 hour. The sulfonate obtained is then transformed "*in situ*" to the sulfonyl chloride of formula VII by contacting with *N*-chlorosuccinimide at a temperature ranging from 0°C to 70°C.

The sulfonamide derivatives of formula I are then prepared from the corresponding above mentioned sulfonyl chloride V or VII, by reaction with a corresponding cyclic amine, e.g. either with a piperazine or piperidine derivative of the general formula VIII or IX.

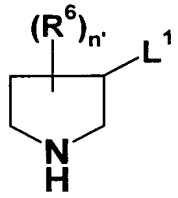


VIII or

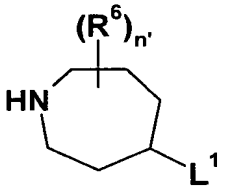


IX

or a pyrrolidine, an azepan or a 1,4-diazepan of the below formulas



or



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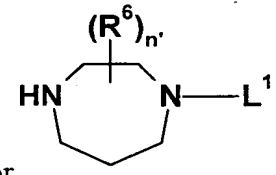


whereby R^6, n L^1 and L^2 are as above defined.

The above set out cyclic amines, notably those of formula VIII or IX are either commercially available compounds or compounds that can be prepared by known procedures.

Typically, piperazines of type VIII can be prepared upon using conventional methods known by a person skilled in the art.

For L^1 and/or L^2 = aryl, suitable methods of preparation are described in *Tetrahedron Lett.* **1996**, *37*, 8487-8488 and references cited therein.

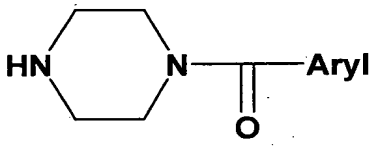
For L^1 and/or L^2 = aryl C_1-C_6 alkyl, a further preferred method is the reaction of the corresponding piperazine or mono-*N*-protected piperazine with compounds of formula X

$$\text{Aryl}—(CH_2)_n—X \qquad X$$

wherein X is Cl, Br, I, OTs, OMs

The reaction is generally conducted in the presence of a base such as triethylamine, diisopropylethylamine, potassium carbonate and the like in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

For L^1 and/or L^2 = -C(S)-, a further preferred method is the conversion of compounds of type XI using the Lawesson's reagent which allows the transformation of an amide into a thioamide group as described in *Bull. Soc.Chim. Belgium*, **1978**, *87*, 229.



XI

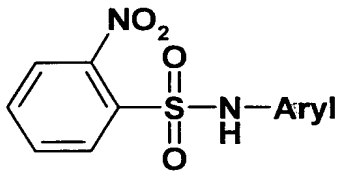
The sulfonamides of formula I are readily prepared by contacting the sulfonyl chlorides V with an amine of formula VIII in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methyl-pyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

Alternatively, the sulfonamide derivatives of formula I are readily prepared from the corresponding sulfonyl chloride V or VII, by reaction with a piperidine of general formula IX. Piperidines of formula IX are either commercially available compounds or compounds that can be prepared by known procedures. Typically, piperidines of type IX can be prepared using conventional methods known by one skilled in the art and described by way of examples in *J. Pharm. Sci.* **1972**, *61*, 1316; *J. Heterocyclic. Chem.*, **1986**, *23*, 73; *Tetrahedron Lett.*, **1996**, *37*, 1297, US 5106983, WO/9113872 and WO/9606609.

Preferred methods of obtaining piperidines of formula IX are the following:
For L^1 = H and L^2 = (CH_2)n-Aryl wherein n = 0,1,2; addition of an organometallic species such as $Ar^3(CH_2)_nLi$ or $Ar^3(CH_2)_nMgBr$ on mono-protected 4-piperidone followed by reduction of the so-formed double bound which allows the formation of compounds of type IX.

For L^2 = -NR-(CH_2)n-Aryl wherein n = 0,1,2, a preferred method is the reductive amination of 4-piperidone with amines of type Aryl-(CH_2)n-NR-H.

A further preferred method in the case where n = 0 is a "Mitsunobu type" coupling between an activated aniline of type XII with mono-N-protected 4-piperidol as described in *Tetrahedron Lett.* **1995**, *36*, 6373-6374.

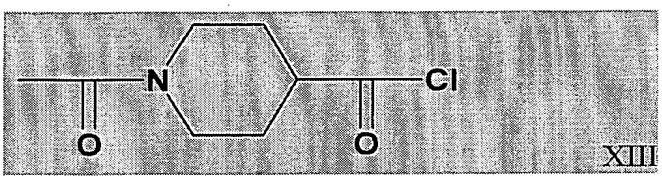


XII

Deprotection of the sulfamino group is then carried out using thiophenol in the presence of potassium carbonate.

For L^2 = -NR^3'C(O)R^3, -NR^3'C(O)NR^3'R^3, NR^3'SO_2-R^3, a preferred method of synthesis of compounds of formula IX is the reaction of commercially available N-BOC-4-aminopiperidine with respectively acyl chlorides, isocyanates and sulfonyl chloride under classical conditions very well known by one skilled in the art.

When L^2 = -CO-Aryl, compounds of formula IX are readily prepared by contacting well chosen aromatic or heteroaromatic rings with intermediate of type XIII



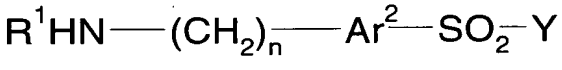
XIII

in the presence of a Lewis acid such as aluminum trichloride or titanium tetrachloride in a polar aprotic solvent such as dichloromethane. Intermediate XIII can be easily obtained by first acetylation of piperid-4-yl carboxylic acid and their formation of the acyl chloride by treatment with thionyl chloride.

The sulfonamides of formula I are readily prepared by contacting the sulfonyl chloride V with an amine of formula IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is pref-

erably conducted in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

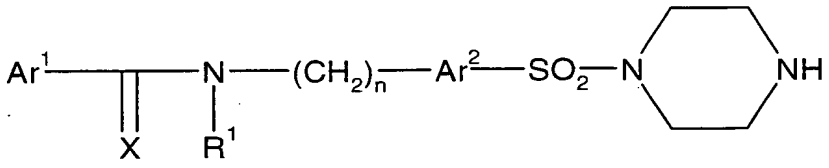
The sulfonamides of formula XIV are readily prepared by contacting the sulfonyl chloride VII with an amine of formula VIII or IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C. The use of sulfonyl chloride of type VII leads to amines that have to be deprotected using well known methods by one skilled in the art to afford amine of general formula XIV



XIV

wherein R^1, Ar^2, Y and n are as above defined.

Derivatives of type XIV are then acylated according to described methods for the preparation of amides by condensation of amines with acid chlorides or carboxylic acids in the prefered conditions described above leading to compounds of general formula I
In the particular case of compounds of general formula I where Y represents a piperazine derivative, an alternative method of preparation which has also to be considered as part of this invention, said method of preparation consisting in the condensation of a piperazine derivative of formula XV



XV

with electrophiles L^1 which will be chosen depending on the nature of L^1 (see the above definition of L^1, L^2). Procedures and methods to perform these types of condensation are well-known and have been well described on various synthesis of N-substituted piperazine derivatives.